

Appl. No. 09,700,806
Amd. dated November 22, 2004
Reply to Office Action of June 21, 2004

REMARKS

Entry of the Amendment and reconsideration of the rejection of the claims in view of the following Remarks is respectfully requested. Applicants submit no issues not previously considered by the Examiner are raised herein.

Claims 1, 10, 14, 15, 19, and 21 have been amended to further clarify the invention. Claims 22-31 are newly presented. Support for the Amendments and newly presented claims can be found on page 4 at lines 4-11, on page 6 at lines 6-12, Table 3 at page 40, and in original claim 2. Claim 10 has been amended to provide proper antecedent basis.

Claims 3, 5-7, 9, 11-13, and 20 were previously withdrawn as being drawn to a non-elected invention. Claims 16 and 17 were withdrawn as being drawn to a nonelected species and are not being cancelled at this time. Similarly, new claims 26-31 also include nonelected species. Upon allowance of a generic claim, Applicants request that the Examiner search the nonelected species.

Claim 18 has been canceled without prejudice or disclaimer. Applicants reserve the right to pursue the subject matter of the cancelled claims in one or more continuation applications.

Therefore, claims 1, 8, 10, 14-15, 19, and 21-31 are pending after entry of the Amendment.

Withdrawn Rejections/Objections

Applicants acknowledge the withdrawal of the rejection of claim 10 under 35 U.S.C. § 112, second paragraph.

Applicants acknowledge the withdrawal of the rejection of claims 1, 8, and 10 under 35 U.S.C. § 112, first paragraph as lacking enablement.

Enablement

Claims 1-2, 8, 10, 14, 15, and 21 are rejected under 35 U.S.C. § 112, first paragraph for alleged lack of enablement. The Examiner contends that the specification does not reasonably enable any VEGF variant or VEGF receptor agonist that selectively binds KDR receptor. Applicants respectfully traverse this rejection.

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The Examiner contends the claims are not enabled because Applicants have not disclosed which residues outside of the KDR receptor binding region or FLT-1 receptor binding region can be mutated to produce VEGF variants or VEGF receptor agonists selective for the KDR receptor. Applicants do not agree.

"For a claimed genus, representative examples together with a statement applicable to the genus as a whole will ordinarily be sufficient [to enable the claims] if one skilled in the art (in view of level of skill, state of the art and the information in the specification) would expect the claimed genus could be used in that manner without undue experimentation. Proof of enablement will be required for other members of the claimed genus only where adequate reasons are advanced by the examiner to establish that a person skilled in the art could not use the genus as a whole without undue experimentation." MPEP 2164.02. Only a reasonable correlation between enablement and the scope of the claims is required.

The claims recite methods for treating nitric oxide (NO) associated disorders, or methods of stimulating sustained production of endogenous NO in an endothelial cell, using VEGF receptor agonists that exhibit selective binding affinity for a KDR receptor. The claimed VEGF receptor agonists comprise a VEGF variant having one or more amino acid substitutions in a loop containing FLT-1 contact residues D63, E64, and E67 and the binding affinity of the agonist for FLT-1 receptor is reduced as compared to the binding affinity of native VEGF for FLT-1 receptor. Applicants submit that the claims are fully enabled, because their scope reasonably correlates with the enablement provided by the disclosure.

Applicants have provided extensive guidance to one of skill in the art concerning the nature of mutations that could be made to obtain a VEGF variant exhibiting selective binding affinity for KDR receptor. Applicants disclosed which regions of VEGF are important for binding to KDR receptor and FLT-1 receptor (page 4, lines 1-22 and Example 6) and provided working examples for a method of producing VEGF variants and selecting for variants exhibiting selective binding affinity for KDR receptor (Examples 6 and 7). Using this method, Applicants obtained and disclosed 29 different variants exhibiting selective binding affinity for KDR receptor (Table 2). The specification further discloses in Table 2 the nature of the differences in amino acid sequence between native VEGF and the variants. Table 3 discloses the selectivity and properties of the variants. With respect to Table 3, Applicants note that the second number in each column indicates the fold difference in binding affinity of the variant

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relative to the control. For example, variant LK-VRB-1s has the same binding affinity for the KDR receptor as the control, while its binding affinity to FLT-1 receptor is 6000-fold less than the VEGF control. Applicants submit, therefore, that the specification provides representative examples of the claimed genus such that the genus is fully enabled.

Even an "extended period of experimentation may not be undue if the skilled artisan is given sufficient direction or guidance." *MPEP 2164.05(b)* (citing *In re Colianni*, 561 F.2d 220, 224 (CCPA 1977)). As discussed above, Applicants provided extensive guidance to one of skill in the art concerning the nature of mutations that could be made to obtain a VEGF variant exhibiting selective binding affinity for KDR receptor and methods of screening variants for selective binding affinity to a receptor are routine in the art. Applicants therefore submit it would not require undue experimentation to obtain other variants within the claimed genus of variants exhibiting selective binding affinity for KDR receptor.

In view of the extensive guidance provided in the specification, Applicants respectfully submit the Examiner has not adequate reasons to establish that a person skilled in the art could not use the genus as a whole without undue experimentation. For the forgoing reasons, withdrawal of the enablement rejection is respectfully requested.


Summary

In view of the above amendments and remarks, Applicant respectfully requests a Notice of Allowance. If the Examiner believes a telephone conference would advance the prosecution of this application, the Examiner is invited to telephone the undersigned at the below-listed telephone number.

Respectfully submitted,

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Date: November 22, 2004


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